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EXTRACORPOREAL DIALYSIS FOR RENAL DISORDERS*

The term "artificial kidney" is a misnomer for the apparatus it describes, since so-called "artificial kidneys" have none of the selective resorptive properties of the mammalian kidney, nor have they any of the metabolic function. Most of the "artificial kidneys" in use today are more properly described as extracorporeal dialyzers. The basic unit in all of these apparatuses is the same: a semipermeable membrane through which diffusible solute can pass. On one side of the membrane, blood from the patient flows; on the other side is placed a properly constituted rinsing fluid. The membrane is generally cellophane, in which the capacity for dialysis can be compared to the normal glomerular membrane in the following parameters (Figure 1).

The membrane is readily permeable to water and to crystalloids of smaller molecular weights, but albumin and protein molecules of larger molecular weight are retained. Unlike the tubular epithelium of the kidney, the membrane is inert, so that the direction and rate of solute transfer depends upon the concentration gradient for these molecules, as well as their diffusion characteristics. "Direction" of solute transfer refers to net change, since the membrane is, of course, freely permeable in both directions. Although potassium molecules, for example, pass both from rinsing fluid into blood and from blood into rinsing fluid, the rate at which transfer occurs will be determined by the difference in concentration on either side of the membrane. Thus, if initially the potassium concentration is 8 mEq./l in blood and zero in the rinsing fluid, net transfer of potassium will take place from blood to bath until a concentration of 4 mEq./l is obtained on each side. If the rinsing fluid is changed frequently, or if the fluid is made to pass the membrane in a continuous flow, equilibrium will never be obtained and large amounts of potassium may be removed by constantly maintaining the gradient from blood to rinsing fluid.

In clinical use of the apparatus, advantage is taken of this fact. The concentration of electrolyte and diffusible substance is so adjusted in the bath fluid as to continue or prevent transfer of substance as a result of the diffusion gradient. If,

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for example, a patient with hyponatremia is treated with extracorporeal dialysis, a normal sodium concentration (140 mEq./l) may be maintained in the bath. If the patient begins dialysis with a serum sodium of 120 mEq./l, sodium will diffuse from bath to blood until a serum concentration of 140 mEq./l is reached. At this time, although sodium ions will continue to go in both directions across the membrane, no net change in serum or bath concentration will result. It can be seen, then, that the direction of solute transfer is determined by diffusion gradient for each solute and is independent of the rate or direction of transfer for other solutes. What this means, from the clinical standpoint, is simply that the serum sodium may be raised at the same time that the serum potassium is decreased, by maintaining appropriate diffusion gradients by the adjustment of the bath concentration of each ion. This ability to change, individually and independently, various serum concentrations at the same time is one of the important advantages of the artificial kidney.

What has been said of solute is also true of water, but water concentration is, of course, a reciprocal of solute concentration in any solution. In this sense, a concentrated solution contains less water and therefore water will move from the less concentrated to the more concentrated solution. The total solute concentration, or the total number of osmotically active particles (osmolality) on either side of the membrane, determines the direction and rate of water exchange. The number of osmotically active particles, or the osmolality, of the solutions determines the rate and direction of water transfer. Thus, the solution with the highest osmolality or the highest osmotic pressure will effect a transfer of water into it from the less concentrated solution. Since the concentration of electrolytes in the rinsing fluid is usually determined by the necessity for resultant changes in the patient's blood, glucose is added to the rinsing fluid to change the total osmolality. Since, however, the membrane is readily permeable to glucose, glucose passes from rinsing fluid into the blood and therefore is not an entirely effective method of increasing the osmolality of the rinsing fluid.

Hydrostatic pressure is another way of effecting water transfer across the cellophane membrane, and a number of "artificial kidneys" take advantage of this principle. In these apparatuses, the cellophane is supported by fiberglass or stainless steel screening, and a pressure gradient is created across the membrane in order to move water out of blood into the rinsing fluid. If no rinsing fluid is placed on the external surface of the cellophane membrane and a hydrostatic pressure gradient is created across this supported membrane, an ultrafiltrate of plasma may be produced. Several of the types of artificial kidney in clinical use today, by employing negative pressure on the external surface of the cellophane membrane may remove as much as 700-1,200 ml. of ultrafiltrate of plasma per hour. The advantage of this technique in the therapy of edema is another application of the so-called "ultrafilter" types of artificial kidney.

The artificial kidney as a clinical and experimental tool has received extensive clinical trial, both in this country and abroad in the past ten years. Six widely used types of apparatus exist today, varying rather markedly in design, but essentially similar in their application of the principles of dialysis and ultrafiltration. All of them employ a cellophane membrane of essentially the same permeability characteristics. Animal membranes have also been used as the basic unit for artificial kidneys, but it is doubtful that these will attain any widespread degree of usefulness. The use of cation exchange resins over which blood flows in the so-called "ion exchange artificial kidney" have been utilized to remove electrolytes selectively. Their usefulness, however, is limited by their relative inefficiency and by the damage to platelets and white cells which occurs.

It is not the purpose of this review to comment upon the relative merits of the various types of artificial kidney. By employing cellophane as the filter, in the hands of skilled physicians all of the six major designs perform the function required of them safely and efficiently. Several of them are available commercially. One of the most widely used (Kolff twin coil, Travenol Laboratories) can be purchased at a moderate price, and prepackaged cellophane units are available, thus facilitating the problem of maintaining and assembling such a unit. Another compact artificial kidney of somewhat different design (Collins) can be purchased complete. However, the availability of an elegant tool for extracorporeal dialysis does not ensure its successful clinical application any more than the availability of a finely made vascular prosthesis ensures the success of an aortic graft. The successful use of an artificial kidney requires a thorough knowledge of the patient and the disease to be treated. A brief consideration of these factors, therefore, would seem appropriate.

As early as 1913, it was suggested by Abel, who published the first description of an artificial kidney, that "There are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of removing from the body, at an adequate rate, the natural or unnatural substances, the accumulation of which is detrimental to life." In the hope of providing a substitute in such emergencies, which might tide over a dangerous crisis, "a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body."[1] It was obvious, therefore, that the artificial kidney should be used as a temporary measure in the treatment of acute renal failure of

various causes, where the renal lesion itself was eventually reversible. It has been widely used in this situation, and the consensus of the physicians using it in this fashion will be summarized.

The artificial kidney, when applied to patients, accomplishes two things and two only: (1) the correction of abnormalities of the composition of body fluids; and (2) the removal of fluid. Insofar as the patient's morbid state is due to abnormalities of body fluid composition, or to overhydration, the artificial kidney may be used successfully to correct these abnormalities. When, however, he is suffering from peritonitis, hemorrhage, or central nervous system damage, the artificial kidney has nothing to offer in the specific relief of these abnormalities. Frequently, however, in infected or traumatized patients with acute renal failure, it is difficult to determine what proportion of the problem is secondary to "uremia" and what to the surgical complications. To the degree that uremia may accentuate the gravity of these other complications, its correction by extracorporeal dialysis may be expected to improve the patient. Since any degree of renal failure cannot improve the clinical situation, but must inevitably make it worse, it can be argued that the use of the artificial kidney may be of value at any stage of renal failure. This argument has been used recently to support use of the artificial kidney once a day for the entire course of the patient's renal failure.[2] The arterial and venous cannulae inserted for dialysis are left in place and kept patent by the hourly injection of a small amount of heparin solution. In the hands of the experienced team by which it has been used, this has been an effective method. It does not seem entirely practicable, however, for general use, although the ultimate aim is certainly an admirable one. In expert hands, the conservative management of acute renal failure has now improved so much that the use of the artificial kidney is less frequently necessary.

However, in spite of the most expert management, patients with prolonged renal failure may become critically ill because of the accumulation of metabolic products ordinarily excreted by the kidney. Hyperkalemia is a common complication of acute renal failure, and potassium intoxication is a not infrequent cause of death. Potassium intoxication is the result not only of potassium retention but concomitant derangements in the concentration of other electrolytes, particularly of hydrogen ion. The correction of all of these abnormalities by dialysis with the artificial kidney may be an important therapeutic adjunct where conservative methods alone are not adequate. Equally important is the amelioration of the "uremic syndrome." We do not know precisely what the "uremic syndrome" is. Certainly, it is due only in small part to the retention of urea. What is apparent, however, is that when retention products which result in the clinical

	CELLOPHANE	GLOMERULAR CAPILLARY
FRACTIONAL PORE AREA	30-45%	1%
TOTAL AREA	22,000 cm.^{2} (Rotating Model)	7600-15,000 cm.^{2}
PORE RADIUS	30 A°	30-45 A°
PORE LENGTH	80μ	1μ

(PORE RADIUS OF 100-120—95% ALBUMIN PERMEABLE)

Figure 1. Cellophane and glomerulus as semipermeable membranes. The cellophane membrane is compared with the glomerulus with regard to its fractional pore area (the area available for transfer of solute), the total area available for filtration, the pore radius (the radius of the theoretic pore through which the molecule must travel) and the pore length. A pore with a radius of 100-120 Angstrom units is 95 per cent albumin-permeable, and thus, as is the case, it would not be expected that the cellophane would permit passage of this molecule. (*From Merrill, J. P.: Treatment of Renal Failure, New York, Grune & Stratton, 1955, p. 186. Reprinted by permission of the publisher.*)

syndrome of uremia are removed through a semipermeable cellophane membrane, this clinical state is ameliorated, and conservative methods of therapy may become more effective. With good conservative methods, the patient may not die of "uremia" alone. However, drowsiness, semicoma, nausea and vomiting predispose such patients to aspiration pneumonia which may prove fatal. In this regard, then, the general improvement in well-being which results from an effective dialysis may contribute considerably to the care of the patient.

The use of the artificial kidney in the treatment of chronic renal failure has been limited. Since the underlying renal disease is not reversible, it is seldom justified to prolong, for brief periods, the life of a terminally ill patient with chronic renal disease. In occasional instances, however, dialysis may be used to tide a patient over the exacerbations of renal disease, or to prepare one for a surgical procedure aimed specifically at improving the renal status. In the patient whose illness is due simply to "uremia," and not to the frequently present hypertensive cardiovascular disease, the artificial kidney may give relief of symptoms when conservative measures are either inadequate or too slow. Such patients must be carefully selected, but in our experience, dialysis has been used satisfactorily in three or four cases a year of this kind.

The use of the ultrafilter types of artificial kidney to remove edema has not been sufficiently explored. An occasional patient refractory to usual methods of diuretic therapy may again become responsive, if part of his massive edema is corrected by the mechanical removal of extracellular fluid. The ultrafilter types of artificial

kidney can accomplish this, and their use should be explored for this clinical problem.

Much has been written about the use of the artificial kidney in the treatment of acute drug intoxication. There is no question that barbiturates, salicylates, bromides, and many other therapeutic agents which can be toxic when ingested in large amounts may be effectively removed by dialysis. As in the evaluation of the artificial kidney for the treatment of acute renal failure, one must consider carefully whether or not conservative measures alone might be adequate. In the present state of our knowledge, we cannot always relate blood levels of these substances to the clinical status. In the patient seen 48 hours after the ingestion of barbiturates, who is comatose but has normal renal function, adequate ventilation, and appears to be progressing satisfactorily, it is doubtful that removal of barbiturate from the blood at this point will contribute enough to make the procedure worth while. On the other hand, the patient seen within hours after taking the drug, who has a very high blood level of barbiturate, impaired renal function, respiration and blood pressure, may profit from the removal of the toxic substance by dialysis. In between these two extremes, each case must be decided on its own merits.

Contraindications, of one degree or another, to the use of the artificial kidney are: (1) inexperience of the operator and inadequate knowledge of the problem to which the apparatus is to be applied; (2) bleeding, particularly bleeding from the gastrointestinal tract, since heparinization is necessary to prevent coagulation of blood in the extracorporeal circulation (it is, however, possible by "regional heparinization" to heparinize blood entering the machine, neutralizing it with protamine sulfate as it returns to the patient's venous circulation—in this way the hazards of bleeding may be minimized); (3) destruction of platelets and white cells by the cellophane membrane during the course of hemodialysis. This is seldom of clinical importance in the individual with a normal white and platelet count. However, it must be considered before undertaking dialysis in patients with any disturbances in these parameters.

In summary, the artificial kidney in any one of its several present forms is an effective and safe method of correcting abnormalities of composition of the extracellular fluid when used by an experienced, competent team. It should always be an adjunct to, rather than a substitute for, the best methods of conservative therapy. Its use to remove ingested toxins may be of benefit where a high blood level of these substances exists, the patient's own renal mechanism is inadequate and the clinical condition critical. Since experience is obtained only by constant use, and since this experience is one of the necessities for effective application, the use of the artificial kidney should probably be confined to those centers where the patient load is great enough to justify its use at least once a week. In institutions which do not have an artificial kidney, many patients are adequately handled with conservative methods alone. When these are not adequate, such patients may be referred for treatment to a center which has had a continuing experience in extracorporeal dialysis.

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